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Depression and anxiety in patients receiving interferon-alpha: the role of illness perceptions

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Abstract

Development of psychiatric symptoms during interferon-alpha (IFN-α) therapy may be influenced by psychological factors. We examined illness perceptions using The Revised Illness Perceptions Questionnaire (IPQ-R) in 55 patients with chronic Hepatitis C virus infection, due to receive IFN-α. The Hospital Anxiety and Depression Scale (HADS) was used to assess the development of symptoms. Negative identity, consequences and emotional representations beliefs were significantly associated with both higher depression and anxiety scores. Negative illness perceptions play a predictive role in the development of IFN-α-induced psychiatric symptoms.

Keywords

Anxiety, depression, illness perceptions, mood, psychological distress, side effects

Introduction

Interferon-alpha (IFN-α) therapy for chronic hepatitis C virus (HCV) infection is associated with the development of depression and other neuropsychiatric adverse effects (Sockalingam and Abbey, 2009). Depression is the most commonly observed neuropsychiatric symptom during IFN-α therapy with an incidence of up to 45% (Asnis and De La Garza, 2006, Capuron and Miller, 2004, Raison et al., 2005b). There has been less focus on the development of anxiety. However, a recent study reported 46.6% of patients met criteria for generalized anxiety disorder following 12 weeks of IFN-α treatment (Bassiony et al., 2015). When the incidence of depressive and anxiety symptoms are combined, the cumulative incidence can be as high as 60% (Evon et al., 2008, Fontana, 2000, Kraus et al., 2003).

In recent years, extensive research has been conducted into understanding and detecting different risk factors associated with the development of neuropsychiatric side effects during IFN-α treatment. Demographic and clinical risk factors for the development of IFN-α-induced depression include a history of major depressive disorder (Castera et al., 2006, Raison et al., 2005a) and the presence of mood or anxiety symptoms prior to treatment (Dieperink et al., 2003, Evon et al., 2009, Lotrich et al.,

2007). More recently, a large-scale study showed that a psychiatric history was a strong risk factor for the development of both depression and anxiety during treatment (Masip et al., 2015). However, little research has focused on understanding the role of psychological factors. Well-defined predictors of the development of IFN-α-induced neuropsychiatric side effects, which are independent from previous or current psychopathology, are still lacking.

A biopsychosocial model of health and illness may be helpful in understanding the psychological distress associated with IFN-α therapy. One of the most widely researched models of health and illness is Leventhal's self-regulatory model. This model emerged from a series of studies where high fear messages were consistently found to be more effective in changing attitudes toward a recommended health action in comparison to low fear messages (Leventhal, 1970). The model is based on the notion that individuals are active problem solvers dealing with the perceived reality of a health threat as well as their emotional reactions to this threat (Leventhal et al., 1980). Accordingly, they make sense of a threat to their health and determine how to respond by developing their own cognitive representations of the threat. These cognitive representations, also known as illness perceptions, are a patient's own common sense beliefs about their

illness. The manner in which patients perceive their illness and subsequent therapy is likely to influence many aspects of their experience including side-effects (such as developing depression or anxiety) and other health outcomes. As such, examining domains of illness perceptions may provide useful information for the development of interventions aimed at reducing the occurrence of these symptoms.

Across disease groups, and particularly in chronic disorders, illness perceptions have been found to be associated with several emotional well-being and quality of life outcomes (Bonsaksen et al., 2015, Endermann and Zimmermann, 2009, Rochelle and Fidler, 2013). A meta-analysis has demonstrated a salient relationship between cognitive illness perceptions and a range of emotion focussed coping behaviours across 23 health conditions (Hagger and Orbell, 2003). In specific conditions such as myocardial infarction, negative illness perceptions have been shown to contribute to the development of subsequent new episodes of depression (Dickens et al., 2008). This has also been demonstrated in chronic conditions such as multiple sclerosis, psoriasis, diabetes and irritable bowel syndrome (Fortune et al., 2002, Jopson and Moss-Morris, 2003, Paschalides et al., 2004, Rutter and Rutter, 2002). Research on individuals with well-defined diseases has shown in particular that a strong illness identity, a long

timeline perspective, and serious consequences are associated with more negative health outcomes (Hagger and Orbell, 2003).

Illness perceptions have not previously been investigated in patients with HCV infection treated with IFN-α. The aim of this study was to test the hypothesis that negative illness perceptions (as defined by a greater number of associated symptoms, greater perceived duration and cyclical nature, more perceived consequences, less perceived personal and treatment control, less illness coherence and greater emotional responses) about HCV infection prior to starting IFN-α therapy will be associated with the development of increased depressive and anxiety symptoms during treatment.

Materials and methods

Study design and participant selection

A prospective cohort design was used to investigate the effects of IFN-α therapy. Patients were evaluated at baseline (week 0) and after 4, 8, 12, 16, 20 and 24 weeks of IFN-α treatment. All data were collected in the presence of a trained researcher during monthly outpatient appointments which participants attended as part of their IFN-α therapy. For convenience, participants were given the option of completing follow-up

self-report questionnaires at home prior to their appointment, followed by a shorter face-to-face interview with a researcher. In these cases, questionnaires were sent to participants via post a few days prior to their appointment and they were then asked to bring their completed questionnaires with them to their appointment. We recruited and assessed a total of 55 participants. Participants were recruited from the outpatient liver departments of three London hospitals: King's College Hospital, Guy's and St. Thomas' Hospital and St. George's Hospital. Eligible participants were adult patients with chronic HCV infection who were due to commence combination antiviral therapy with IFN-α and ribavirin. All patients were scheduled to receive combination therapy for at least 24 weeks. This comprised of weekly subcutaneous IFN-α injections (1.5 µg per kg of body weight) and daily ribavirin tablets (800 to 1400 mg orally per day in 2 divided doses). Exclusion criteria included age below 18 years, autoimmune disorder, cause for liver disease other than HCV, current use of antidepressants, lack of English language and co-infection with HIV or hepatitis B. Written informed consent was obtained from all participants after a complete explanation of the study, a presentation of a participant information sheet and an opportunity to ask questions. The study was approved by the King's College Hospital Research Ethics Committee (Ref: 10/H0808/30).

Sociodemographics and psychiatric history

In order to identify potential risk/predictive factors for the development of IFN-α-induced depression and anxiety, some assessments were conducted by a trained interviewer at the baseline, immediately before IFN-α therapy. These included the collection of socio-demographic data using a modified version of the MRC Sociodemographic Schedule (Mallett et al., 2002). Dichotomised variables were created to consolidate multiple classes of data for: ethnicity; level of education; current relationship status and current employment status. A previous history of major depressive disorder was assessed using the relevant section of the Mini International Neuropsychiatric Interview (MINI). The MINI is a structured diagnostic interview for psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (Sheehan et al., 1998).

Measure of illness perceptions

Information regarding illness perceptions was collected using The Revised Illness Perceptions Questionnaire (IPQ-R) (Moss-Morris et al., 2002). We used the first two sections of the IPQ-R: the first section examines illness identity (the symptoms the

individual associates with the illness) and the second section examines participants' beliefs about their illness. This second section is comprised of the domains of timeline (acute/chronic and a cyclical subscale), consequences (expected effects and outcome), personal and treatment control (beliefs about potential for cure and control of the illness), illness coherence and emotional representations (Weinman et al., 1996). Higher scores indicate a strong identity, perception that the illness is chronic and that it is cyclic in nature, that it has serious consequences, that control or cure is possible, that the individual has a good understanding of their illness and a strong emotional response.

Measure of depressive and anxiety symptoms

The presence and severity of depressive and anxiety symptoms were assessed at baseline and at every subsequent monthly assessment during the course of IFN-α therapy using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The HADS is a widely used 14-item self-report scale designed to briefly measure current anxiety and depressive symptomatology in non-psychiatric hospital patients. It excludes somatic symptoms, therefore avoiding potential confounding by somatic symptoms. There are independent subscales for anxiety and depression each comprised of 7-items designed to screen for the presence and severity of symptoms over the past

week. Items are scored on a 0-3 scale to give a total score range of 0-21. Scores in the range of 0-7 are considered normal; 8-10, mild; 11-14, moderate; and 15-21, severe.

Data analyses

Data were analyzed using IBM SPSS statistical software version 20 and STATA version 11. Continuous variables are presented as mean ± standard errors. Pearson correlation analyses and one-way analyses of variance were conducted to evaluate continuous and categorical variables as covariates of depression and anxiety scores. Given the relatively small sample size, only significantly correlated variables were retained as covariates in the main regression analyses. Random intercept regression models with maximum likelihood effects were used to investigate the predictive effects of illness perceptions dimensions on changes in depression and anxiety scores as a function over time. The dataset is changed from wide to long format and clustered by individual. This method of analysis is an ideal way to model repeated measures.

Results

Sample characteristics and symptomatology

All 55 participants completed the baseline and three follow-up assessments (up to treatment week 12). The socio-demographic and disease characteristics of the sample are presented in Table 1. The disease characteristics include: HCV genotype, baseline viral load (that is, the number of viral particles per ml of blood presented in millions) and the severity of liver disease as measured by a fibroscan and rated in kilopascals (KPa). At baseline, no participants met criteria for a current MDD diagnosis. However, 18 participants (33%) had a self-reported history of MDD and 14 (26%) had a family history of psychiatric illness. Both depression and anxiety scores increased significantly over the course of IFN-α treatment (Coefficient=0.14, $p<0.001$ and Coefficient=0.04, $p=0.027$, respectively). The proportion of participants meeting criteria for mild, moderate and severe depression and anxiety during IFN-α therapy is presented in Table 2. Only 2 participants were started on anti-depressant treatment during the course of the study.

[INSERT HERE TABLE 1]

[INSERT HERE TABLE 2]

Covariates of depression and anxiety

In line with findings from previous studies, baseline depression scores were associated with subsequent depression scores at all treatment weeks (r=0.46-0.58, all p<0.01) and with subsequent anxiety scores at all treatment weeks (r=0.35-0.56, all p<0.01). Similarly, baseline anxiety scores were associated with subsequent depression scores specifically at treatment weeks (TW)4, TW12, TW20 and TW24 (r=0.35, r=0.36, r=0.33, r=0.44, respectively, all p<0.05) and with subsequent anxiety scores at all treatment weeks (r=0.51-0.63, all p<0.01). A previous history of depression was associated with subsequent anxiety scores at TW4, TW8, TW16 and TW20 (F=5.98, F=10.24, F=6.71, F=4.56, respectively all p<0.05) but not with depression scores. Furthermore, age was also negatively associated with subsequent anxiety scores at TW4 and TW8, (r=-0.29 and r=-0.33, both p<0.05) but again not with depression scores. As such, baseline depression scores, baseline anxiety scores, previous history of depression and age were retained as covariates in subsequent regression analyses for anxiety. Only baseline depression scores and baseline anxiety scores were retained as covariates for subsequent regression analyses for depression. No other socio-demographic factors were associated with either depression or anxiety scores.

Illness perceptions as predictors of depression

To establish illness perceptions domains as possible predictors of higher depression scores, we ran a separate regression analysis for each illness perceptions domain, adjusting for relevant covariates (baseline depression scores and baseline anxiety scores). The results demonstrated that, even after adjusting for these covariates, three illness perceptions domains (identity, consequences and emotional representations) continued to account for significant variance in depression scores with a trend also for the timeline domain (See Table 3).

[INSERT HERE TABLE 3]

Illness perceptions as predictors of anxiety

To establish illness perceptions domains as possible predictors of higher anxiety scores, we again ran a separate regression analysis for each illness perceptions domain, adjusting for relevant covariates (baseline depression scores, baseline anxiety scores, previous history of depression and age). The results demonstrated that, even after adjusting for these covariates, four illness perceptions domains (identity, consequences,

timeline cyclical and emotional representations) continued to account for significant variance in anxiety scores (See Table 4).

[INSERT HERE TABLE 4]

Discussion

This is the first study to investigate the role of illness perceptions on the development of depressive and anxiety symptoms during interferon-alpha (IFN-α) treatment. We demonstrate predictive effects of illness perceptions on higher depression and anxiety scores during treatment. Specifically, we show that negative beliefs in the identity, consequences, timeline cyclical, and emotional representations dimensions predict higher anxiety scores, with identity, consequences and emotional representations also having a predictive effect on higher depression scores. In other words, having a strong illness identity, believing your illness will have more serious consequences and having a strong emotional response to your illness, are all predictive of both depression and anxiety. Moreover, we demonstrate that these effects are independent of previous psychopathology.

These findings are in keeping with previous studies conducted in other populations also showing associations between illness identity as well as strong perceived consequences and timeline to be predictive of poorer health outcomes (Bijsterbosch et al., 2009, Foster et al., 2008, Keeling et al., 2013, Scharloo et al., 2000). Studies examining psychological adjustment to illness have also shown that patients who perceive their illness as having serious consequences, a strong illness identity and chronic timeline have negative associations with physical, social and role functioning (Heijmans and de Ridder, 1998, Scharloo et al., 1998). Previous research has also demonstrated the impact of illness perceptions on outcomes following medical treatment. Again, more negative perceived consequences were shown to be associated with poorer emotional well-being outcomes in men following cancer treatment (Traeger et al., 2009). A recent meta-analysis on diabetes, a condition which presents frequent comorbidity with depression and anxiety, also showed increased beliefs about consequences to be associated with poorer emotional health symptoms as demonstrated by higher depression scores (Hudson et al., 2014). The authors also found identity and timeline beliefs to be associated with anxiety but not depression which, like our findings, suggest there may be differences across emotional states. In the context of HCV infection, it is possible that negative illness perceptions may be influenced by the associated stigma. Indeed, a recent qualitative study investigating patient experiences of undergoing IFN-α treatment in

those with a history of mental health problems, identified stigma and fear of being judged as a key theme (Ware et al., 2015).

There may be biological and psychological underlying mechanisms which potentially drive the association between negative illness perceptions and higher depression and anxiety scores. Two possible (not mutually exclusive) biological mechanisms are increased inflammation and abnormal hypothalamic-pituitary-adrenal (HPA) axis activity. Alterations of the stress response system indicated by abnormal HPA axis activity, is a well-established and consistent finding in depression (Pariante and Miller, 2001). Similarly, there is also a wealth of evidence to support the role of psycho-neuroimmunological dysfunctions in the pathophysiology of depression where there is activation of the immune system (Zunszain et al., 2012). Negative emotions are linked to the immune system's adaptive reactions (Steptoe et al., 2008) and much like other psychological factors, it is possible that negative illness perceptions relate to immune processes in ways similar to general stress. Psychological factors which may underlie the association between illness perceptions and increased depression and anxiety may include personality traits. Previous research has identified neuroticism to be a predictor of IFN-α-induced depression (Lotrich et al., 2007). This is relevant to our findings as

neuroticism is associated more generally with pessimism and negative cognitions and beliefs. Interestingly, neuroticism has also been shown to be associated with increased inflammation (Bouhuys et al., 2004) as well as increased awakening cortisol response (Bhagwagar et al., 2005) again suggesting that there is an interplay between psychological and biological domains.

These findings are of clinical importance as, unlike other factors such as socio-demographic variables, these links between beliefs and treatment induced neuropsychiatric symptoms provide potential for developing preventive cognitive based interventions. Identifying negative thinking associated with the development of psychiatric symptoms could help to develop an intervention targeted towards fostering more adaptive models and expectations, in order to improve outcomes. Indeed, in other populations, interventions aimed at changing illness perceptions have been shown to improve functional health outcomes. For example, a brief hospital intervention designed to alter patients' illness perceptions has been shown to improve functional outcomes and rate of return to work following myocardial infarction (Petrie et al., 2002). A randomized controlled trial of a psychological family-based intervention targeting negative and/or inaccurate illness perceptions in patients with type 2 diabetes, found

that physical health outcomes as well as psychological well-being were improved in the intervention group (Keogh et al., 2011). More recently, a brief cognitive behavioural therapy (CBT) intervention in patients with irritable bowel syndrome (IBS) was shown to change illness perceptions and improve IBS symptom severity (Chilcot and Moss-Morris, 2013). In the context of HCV infection and IFN-α therapy, given that prophylactic treatment with antidepressants is not always effective and carries risk (Galvao-de Almeida et al., 2010, Wu et al., 2007), identifying such targets for clinical intervention is imperative. Of note is also that, identifying predictors of IFN-α-induced depression can still have a role in clinical practice, even in light of emerging IFN-α free treatment regimens. Although, there are new IFN-α free treatment licenced for use in HCV infectious (Ryder, 2015), these treatments are not yet readily available for all viral genotypes. Furthermore, while these new treatments are highly effective, they are expensive. This is a major barrier to access and indeed some have not been approved for use in some countries simply due to the financial burden (Ryder, 2015). As such, IFN-α-induced depression still remains a clinical burden.

There are a few methodological considerations and study limitations that need to be considered in the interpretation of these findings. Information about diagnosis of viral

illness or duration of untreated HCV infection was not collected. This may be of particular importance with regards to illness perceptions, as there may be differences between individuals who have had a more recent diagnosis when compared to those who have had a longer duration of illness. A second limitation of the study is that the baseline assessment was conducted on the first day of treatment, immediately before the first administration of IFN-α. As such, it is possible that some of the baseline psychopathological ratings as well as illness perceptions responses may have been affected by patients' concerns and anxieties surrounding starting IFN-α treatment. A baseline assessment that is more remote from the beginning of therapy initiation may be more appropriate. It is also important to note that due to the high number of predictor variables, there is a potential for increased type 1 error as multiple comparisons were not corrected for. However, frequently used procedures such as the Bonferroni method are conservative, not appropriate for a large number of tests and diminish statistical power (Bland and Altman, 1995). Furthermore, methods to adjust for multiple testing are rare in studies such as this which collect repeated measurements as these comparisons occur for between-subject factors, within-subject factors, or both (Bender and Lange, 2001).

Nevertheless, our study provides evidence for the first time, for a role of illness perceptions in the development of increased depression and anxiety symptoms following IFN-α therapy. Asking patients about their beliefs and understanding of their HCV infection prior to starting treatment, may help to identify more vulnerable individuals who require additional support during the treatment process.

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Table 1. Socio-demographic and disease characteristics of the sample

	Patients *n* **= 55**
Age (years)	
Mean±SEM	44.4±1.6
Range	18-68
Gender	
Males	42 (76%)
Ethnicity	
White British	27 (49%)
Other	28 (51%)
Education Level	
University/A Levels	21 (40%)
GCSEs/No Qualifications	32 (60%)
Employment	
Full-time	31 (56%)
Unemployed	24 (44%)
Relationship Status	
Single	26 (47%)
Married/Cohabiting	29 (53%)
History of Depression	18 (33%)
Family History of Psychiatric Illness	14 (26%)
HCV Genotype	
1&4	12 (22%)

2&3	43 (78%)
HCV Viral Load (million) Mean±SEM	2.1±0.4
Fibroscan (kpa) Mean±SEM	9.8±1.2

Table 2 Proportion of participants meeting criteria for mild, moderate or severe depression and anxiety during the course IFN-α therapy as indicated by HADS scores

	Baseline	TW4	TW8	TW12	TW16	TW20	TW24
Depression							
Normal	89%	76%	69%	64%	58%	59%	70%
Mild	7%	16%	18%	16%	23%	18%	7%
Moderate	4%	6%	7%	13%	15%	14%	16%
Severe	0%	2%	6%	7%	4%	9%	7%
Anxiety							
Normal	81%	82%	73%	76%	73%	68%	71%
Mild	6%	9%	14%	7%	15%	11%	11%
Moderate	11%	7%	11%	13%	8%	14%	13%
Severe	2%	2%	2%	4%	4%	7%	5%

Table 3. Random intercept regression models for depression with maximum likelihood effects (controlled for baseline depression and baseline anxiety scores)

IPQ Dimension	Coefficient	Standard Error	p value
Identity (0-14)	0.24	0.12	**0.050**
Timeline (0-30)	0.14	0.08	0.054
Consequences (0-30)	0.19	0.07	**0.007**
Personal control (0-30)	-0.11	0.13	0.392
Treatment control (0-25)	-0.13	0.13	0.329
Illness coherence (0-20)	0.02	0.11	0.866
Timeline Cyclical (0-20)	0.17	0.10	0.073
Emotional Representations (0-30)	0.16	0.08	**0.047**

Table 4. Random intercept regression models for anxiety with maximum likelihood effects (controlled for baseline depression and baseline anxiety scores, previous history of depression and age)

IPQ Dimension	Coefficient	Standard Error	p value
Identity (0-14)	0.26	0.10	**0.008**
Timeline (0-30)	0.09	0.07	0.157
Consequences (0-30)	0.13	0.06	**0.025**
Personal control (0-30)	-0.15	0.11	0.159
Treatment control (0-25)	-0.10	0.12	0.377
Illness coherence (0-20)	0.06	0.09	0.483
Timeline Cyclical (0-20)	0.18	0.09	**0.033**
Emotional Representations (0-30)	0.14	0.07	**0.040**